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Exposure to magnetic fields and childhood acute lymphocytic leukemia in São Paulo, Brazil

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ABSTRACT

Background: Epidemiological studies have identified increased risks of leukemia in children living near power lines and exposed to relatively high levels of magnetic fields. Results have been remarkably consistent, but there is still no explanation for this increase. In this study we evaluated the effect of 60 Hz magnetic fields on acute lymphocytic leukemia (ALL) in the State of São Paulo, Brazil. *Methods*: This case–control study included ALL cases ($n = 162$) recruited from eight hospitals between January 2003 and February 2009. Controls ($n = 565$) matched on gender, age, and city of birth were selected from the São Paulo Birth Registry. Exposure to extremely low frequency magnetic fields (ELF MF) was based on measurements inside home and distance to power lines. *Results*: For 24 h measurements in children rooms, levels of ELF MF equal to or greater than 0.3 microtesla (μT), compared to children exposed to levels below 0.1 μT showed no increased risk of ALL (odds ratio [OR] 1.09; 95% confidence interval [95% CI] 0.33–3.61). When only nighttime measurements were considered, a risk (OR 1.52; 95% CI 0.46–5.01) was observed. Children living within 200 m of power lines presented an increased risk of ALL (OR 1.67; 95% CI 0.49–5.75), compared to children living at 600 m or more of power lines. For those living within 50 m of power lines the OR was 3.57 (95% CI 0.41–31.44). *Conclusions*: Even though our results are consistent with the small risks reported in other studies on ELF MF and leukemia in children, overall our results do not provide support for an association between magnetic fields and childhood leukemia, but small numbers and likely biases weaken the strength of this conclusion.

1. Introduction

Worldwide leukemia is the most common malignancy in childhood and acute lymphocytic leukemia (ALL) is the most frequent type, around 80% of all pediatric leukemia [1]. In the last two decades, studies from Asia, Europe and North America have reported increased leukemia incidence rates in children, particularly ALL [2–5]. While most accept that the increase in childhood leukemia is real, the reasons are not well understood. Although some of this increase may be due to improvements in the disease reporting and diagnosis, these facts only partly explain the trend. One hypothesis is that this trend might be related to factors linked to modern developments in society.

Many factors have been suggested which could increase the incidence of leukemia in children, but only ionizing radiation is recognized as a risk for ALL and acute myeloid leukemia [6]. In

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1979, Wertheimer and Leeper [7] reported an increased risk of leukemia and brain tumors in children living near power lines. Since then, numerous epidemiological studies of extremely low frequency magnetic fields (ELF MF) have been performed in various countries. Of note are two pooled analyses, one conducted by Greenland et al. [8], which aggregated 12 case–control studies, and reported odds ratio (OR) of 1.7 (95% confidence interval [95% CI] 1.2–2.3) for those exposed to levels higher than 0.3 μT compared with levels lower than 0.1 μT; and another conducted by Ahlbom et al. [9] with nine case–control studies and an OR of 2.0 (95% CI 1.3–3.1) in the highest exposure category (levels equal to or higher than 0.4 μT).

Based on the evidence, particularly results from both pooled analyses, the International Agency for Research on Cancer (IARC) classified ELF MF as class 2B, or as possibly carcinogenic to humans [10]. In 2007, the World Health Organization Environmental Health Criteria confirmed the IARC classification of the epidemiological evidence for childhood leukemia [11].

While studies on the effect of ELF MF exposure on childhood leukemia have been conducted in many countries, none have been done in South America. In this study we evaluated the effect of exposure to 60 Hz magnetic fields on the occurrence of ALL in children living in the State of São Paulo, Brazil.

2. Materials and methods

This case–control study included incident cases of ALL diagnosed from January 1st, 2003 to February 20th, 2009 and born on January 1st, 2000 or later. In order to be included in the study, the child with ALL had to have lived in the State of São Paulo. A maximum period of six months residence outside the State of São Paulo was allowed. Visits to the homes of cases and controls for measurements of ELF MF were performed from February 15th, 2006 to March 25th, 2009.

2.1. Selection of cases

Cases were recruited from eight hospitals, which concentrate on the care of children with cancer and cover more than 50% of all leukemia cases in children in the State of São Paulo. ALL diagnosis was based on clinical patterns, results from blood analysis, immunophenotyping, and when available, cytogenetic and molecular biology analysis.

The mother of the child with ALL (or alternatively the father or other responsible person) was interviewed in the hospital using a structured questionnaire. In each hospital, a member of the clinical staff was responsible for conducting the interviews. Cases that moved post diagnosis were excluded from the study as it was impossible to conduct ELF MF measurements in the homes were they had lived prior to diagnosis, i.e., during the relevant etiologic period.

A total of 248 eligible cases were reported from the hospitals, but 55 (22.2%) had moved from the residence of ALL diagnosis and 14 (5.6%) could not be located and therefore could not be visited for measurements. From the 179 remained cases, 17 (9.5%) refused participate in the study.

2.2. Selection of controls

From the State of São Paulo Birth Registry we tried to obtain four controls matched to case on gender, age (±25% for age below 4 years; ±1 year for age above 4 years) and city of birth, when no controls were available in case's city of residence, controls were selected from adjacent municipalities, but always within the State of São Paulo.

Twenty eligible potential controls, if available, were listed for each case from the State of São Paulo Birth Registry. Then, four were drawn at random for home visit. The interviewers received the list of controls already in the order they should be interviewed. The list of controls was prepared at random by a field coordinator who was unaware of the address location and if it was near a power line or not. In short, neither the person who prepared the list of controls, nor the interviewer knew the location of the controls address prior to selection. If some of four controls were not found after two visits, replacement controls were selected at random from the list. This process continued, when possible, until four controls were selected for each case.

From the 2500 potential controls selected for visits, we ascertained that 1108 (44.3%) had moved, 747 (29.9%) were absent, and three (0.1%) were excluded from the analysis as they had lived outside the State of São Paulo for more than six months. From the 642 remained controls contacted, 77 (12%) refused to participate in the study. As a result, a total of 565 controls were interviewed and ELF MF exposure measurements were made in their homes.

For the 162 participating cases, the number of controls per case varied from zero to four. For 117 cases (72.2%) four controls were obtained, for 22 (13.6%) three, for 12 (7.4%) two, and for seven cases (4.3%) only one control was available. For four cases (2.5%) controls could not be found.

Each household was visited to interview the mother (or father or other responsible person) using a questionnaire similar to the one used for cases. Children selected as potential controls, but with a previous history of leukemia or other cancers were excluded from the study.

2.3. Assessment of exposure to ELF MF

Two approaches were used to evaluate exposure to ELF MF. First, ELF MF exposure measurements were made inside case and control homes using a portable EMDEX-II dosimeter (40–800 Hz, Enertech, Campbell, CA, USA). Measurements of 3 min duration were taken outside the front door and in each room of the house. Subsequently, the dosimeter was left under the child's bed for 24 h. Dosimeters were checked every week and calibrated every six months. The 24 h in home ELF MF were categorized for analysis into less than 0.1 μT, 0.1 μT to less than 0.3 μT, and equal to or greater than 0.3 μT, also levels equal to greater than 0.4 μT were analyzed.

In the second approach, the distance was calculated between case and control households and the closest 88, 138, 230, 345, or 440 kilovolt (kV) power lines. This procedure was restricted to the subset of cases and controls living in the Metropolitan Region of São Paulo (MRSP) because this was the only region in the State of São Paulo where electric grid maps were available. MRSP has a network of 572 km of power lines. A Global Positioning System (GPS) was used to spatially locate each house address. GPS measurements were transferred to a computerized database and then distances of the household to power transmission lines were calculated using MapInfo software for geographical information systems (GIS). We used the distance stratification by Draper et al. [12]: distance of households from power lines was categorized into below 100 m, 100 to less than 200, 200 to less than 600, and equal to or greater than 600 m. We also examined the risk of ALL for those living less than 50 m from power lines; as well as the risk of those living near 88 kV power lines and those living near higher voltage power lines, as the magnetic fields in general are higher in proximity to higher voltages.

2.4. Comparison between cases and controls participating and not participating in the study

Table 1 compares cases and controls not included for any reason with those included in the study. No differences were observed in

Table 1
Cases and controls not included and included in the study compared by demographical variables, living region, distance of home to power line and levels of magnetic fields exposure.

	Cases					Controls				
	Not included[a]		Included		*p* Value	Not included[a]		Included		*p* Value
	n = 113	%	*n* = 162	%		*n* = 1935	%	*n* = 565	%	
Sex										
Male	59	52.2	86	53.1	0.886	963	49.9	297	52.6	0.274
Female	54	47.8	76	46.9		965	50.1	268	47.4	
Age at interview										
<2 years	11	9.8	41	25.3	<0.001	239	12.4	96	17.0	0.019
2 to <4 years	33	29.5	53	32.7		495	25.8	154	27.3	
4 to <6 years	44	39.3	57	35.2		674	35.1	183	32.4	
6 or more years	24	21.4	11	6.8		514	26.7	132	23.4	
Living region										
MRSP[b]	53	49.5	121	74.7	<0.001	1591	82.3	418	74.0	<0.001
Other regions[c]	37	34.6	41	25.3		342	17.7	147	26.0	
Other states	17	15.9								
Distance of home to power line (m)[d]										
≥600	51	96.2	86	71.1	<0.001	1181	74.2	281	67.3	0.025
200–599	1	1.9	20	16.5		270	17.0	88	21.1	
100–199	0		10	8.3		78	4.9	25	6.0	
<100	0		5	4.1		59	3.7	24	5.7	
Missing	1	1.9				3	0.2			
External measurements[e]										
<0.1 μT	20	64.5	96	59.3	0.675	885	47.7	315	55.9	0.002
0.1 to <0.3 μT	7	22.6	49	30.2		683	36.8	171	30.4	
≥0.3 μT	4	12.9	17	10.5		289	15.5	77	13.7	

[a] All reasons. See text.
[b] Metropolitan Region of São Paulo.
[c] Other regions of São Paulo State.
[d] Only cases and controls from the Metropolitan Region of São Paulo (MRSP).
[e] External measurements conducted at the household front door.

gender; however, not participating children were older than participating children. There were also some region differences of residence between included and non-included cases and controls; a higher percentage of participating cases and lower percentage of participating controls were from the MRSP. Higher portions of cases and controls included in the study lived closer to power transmission lines than those not included. While front door measurements did not differ between participating and not participating cases, a higher percentage of included controls had lower front door measurements (ELF MF exposures lower 0.1 μT) than non-included controls.

2.5. Statistical analysis

We performed conditional and unconditional logistic regression analysis, as the results were equivalent we presented only results from the conditional logistic regression analysis. We calculated the odds ratios and respective 95% CI to evaluate the effect of ELF MF exposure and ALL incidence. Analysis was performed using SAS® and SPSS® software. Potential confounding variables, such as age, gender, race (white/non-white), mobility, schooling of the interviewed, Down syndrome, child's history of influenza, child's attendance in day care or school, age of mother at interview, mother's history of work in agriculture, and mother's history of smoking tobacco and alcohol consumption were examined by adding covariates to the conditional logistic regression models.

3. Results

Table 2 shows some additional characteristics of the 162 cases and 565 controls included in the analysis. The majority of cases and controls was classified as white. The prevalence of Down syndrome was higher in cases. Most interviews were carried out with the child's mother. 51.3% cases and 60.4% controls had nine or more years of schooling. Considering study logistics, and as expected, the rate of children who had moved was higher for cases (42.0%) than controls (5.8%).

Mean 24 h ELF MF exposure levels measured under children's beds were comparable for cases (0.104 μT, standard deviation [SD] 0.190 μT) and controls (0.113, SD 0.130 μT). No increased risk was observed in the crude and adjusted analysis for those exposed to

Table 2
Characteristics of participating cases and control.

Variables	Cases		Controls	
	n = 162	%	*n* = 565	%
Race				
White	102	63.0	372	65.8
Non-white	59	36.4	189	33.5
Missing	1	0.6	4	0.7
Number of brothers and sisters				
None	47	29.0	127	22.5
Only 1	50	30.9	227	40.2
≥2	64	39.5	211	37.3
Missing	1	0.6	0	–
Down syndrome				
Yes	6	3.7	4	0.7
No	135	83.3	549	97.2
Missing	21	13.0	12	2.1
Interviewed person				
Mother	153	94.4	441	78.1
Father	5	3.1	39	6.9
Other	4	2.5	85	15.0
Schooling of interviewed person (years)				
Never	5	3.1	9	1.6
<4 years	20	12.3	83	14.7
5–8 years	54	33.3	132	23.4
9–11 years	55	34.0	162	28.7
12 or more	28	17.3	179	31.7

Table 3
Risks (crude and adjusted) of acute lymphocytic leukemia according to exposure to magnetic fields measurements (24 h and night exposure) inside the house by dosimeter, São Paulo State.

μT	Cases		Controls		Crude OR[a] (24 h exposure)[b] (95% CI)[c]	Adjusted OR[d] (24 h exposure)[b] (95% CI)[c]	Adjusted OR[d] (night exposure)[e] (95% CI)[c]
	n = 162	%	*n* = 565	%			
All cases and controls							
<0.1	113	69.8	394	69.7	1.00	1.00	1,00
0.1 to <0.3	38	23.5	137	24.2	0.97 (0.64–1.47)	0.75 (0.36–1.55)	0.48 (0.21–1.11)
≥0.3	11	6.7	34	6.0	1.13 (0.55–2.30)	1.09 (0.33–3.61)	1.52 (0.46–5.01)
Only cases and controls that never moved of household[e]							
<0.1	68	72.3	373	70.0	1.00	1.00	1,00
0.1 to <0.3	22	23.4	125	23.5	0.97 (0.57–1.63)	0.98 (0.39–2.49)	0.50 (0.17–1.45)
≥0.3	4	4.3	35	6.6	0.63 (0.22–1.82)	0.98 (0.18–5.48)	1.72 (0.30–9.87)

[a] Odds ratio.
[b] Average of exposure measurements for 24 h.
[c] 95% confidence interval.
[d] Odds ratio adjusted in the logistic regression model according to age, gender, race (white/non-white); mobility (never moved/moved at least once); education of interviewed person (years of formal schooling); day care (attended/not attended); Down syndrome (no/yes); influenza history (no/yes); age of the mother at interview; mother's history of agricultural work during lifetime (never/ever); mother's history of smoking (never, former, current); mother's history of alcohol consumption (never, former, current).
[e] Average of exposure measurements at night: from 8.00 PM to 8:00 AM. In this analysis was excluded the variable mobility.

levels equal to or higher than 0.3 μT (Table 3). When only considering measurements at night an increased adjusted risk was observed for those exposed at levels equal to or greater than 0.3 μT; and this risk was even higher in analysis that only included cases and controls who had never moved (Table 3). However, estimates were imprecise and included a null value and risk deficits were observed in the intermediate category, with exposures from 0.1 to <0.3 μT. For those exposed to levels equal to greater than 0.4 μT, the adjusted OR were 1.01 (95% CI 0.23–4.42) and 0.18 (95% CI 0.1–3.20), respectively for 24 h exposure and night exposure (data not shown).

Only five cases and 24 controls lived within 100 m of power lines. These numbers dropped to four cases and 11 controls when the distance was within 50 m. Increased risk of ALL was observed for children living within 100 m from power lines and between 100 and 200 m in the MRSP (Table 4). When analysis was restricted to cases and controls who had had never moved, the risk was higher for children living between 100 and 200 m, but remained unchanged for those closer than 100 m from power lines. For those within 50 m of power lines the OR was 3.57 (95% CI 0.41–31.44; data not shown), but based on only four cases. A risk deficit was observed at distance of 200 to 599 m. Most cases (72.6%) and controls (81.2%) had lived close to 88 kV lines. Analysis restricted to this group showed a risk for those living 100–200 m from power lines (OR 4.04; 95% CI 0.70–23.38) and a risk deficit for those within 100 m from power lines (OR 0.39; 95% CI 0.01–15.85). For those who had lived close to >88 kV power lines, risk calculation was not possible due to the small number of observations (data not shown).

4. Discussion

We did not observe increased risk of ALL for exposures equal to or greater than 0.3 μT estimated by 24 h measurements in children's bedrooms. However, when analysis was restricted to nighttime bedroom measurements an increased risk was observed at the same exposure level. When restricted to cases and controls who never moved, nighttime exposure risk was even higher. This result of risk of leukemia in children exposed to higher levels of ELF MF during night is analogous to that reported in Germany, but not in Canada, United Kingdom, or United States [13].

We observed increased risk of ALL among children living within 50 m from power lines, for distances of less than 100 m and at distances from 100 to 200 m. Several former studies have found a relationship between distance of household to power lines and risk

Table 4
Risks(crude and adjusted) of acute lymphocytic leukemia by distance of household to the closest power transmission line, Metropolitan Region of São Paulo.

Distance	Cases		Controls		Crude OR[a] (95% CI)[b]	Adjusted OR[c] (95% CI)[b]
	n = 121	%	*n* = 418	%		
All cases and controls						
≥600	86	71.1	281	67.2	1.00	1.00
200 to <600	20	16.5	88	21.1	0.74 (0.43–1.28)	0.69 (0.28–1.71)
100 to <200	10	8.3	25	6.0	1.31 (0.60–2.83)	1.67 (0.49–5.75)
<100	5	4.1	24	5.7	0.68 (0.25–1.84)	1.54 (0.26–9.12)
Only cases and controls that never moved of household[d]						
≥600	53	72.6	266	67.2	1.00	1.00
200 to <600	9	12.3	85	21.5	0.53 (0.25–1.12)	0.91 (0.25–3.25)
100 to <200	9	12.3	22	5.6	2.05 (0.90–4.71)	3.68 (0.68–19.82)
<100	2	2.8	23	5.7	0.44 (0.10–1.91)	1.52 (0.11–21.24)

[a] Odds ratio.
[b] 95% confidence interval.
[c] Odds ratio adjusted in the logistic regression model according to age, gender, race (white/non-white); mobility (never moved/moved at least once); education of interviewed person (years of formal schooling); day care (attended/not attended); Down syndrome (no/yes); influenza history (no/yes); age of the mother at interview; mother's history of agricultural work during lifetime (never/ever); mother's history of smoking (never, former, current); mother's history of alcohol consumption (never, former, current).
[d] In this analysis was excluded the variable mobility.

of childhood leukemia. Particularly, Draper et al. [12] have found increased risk of leukemia among children living within 200 m of power lines, however, and without a cogent explanation, an increased risk persisted at distances between 200 and 600 m, far beyond the distances where no higher ELF MF are expected. The majority of children in the MRSP lived near 88 kV power lines. When we restricted the analysis to this subgroup of children the risk for those living between 100 and 200 m increased substantially, however fields from low voltage lines are expected to be less than fields at corresponding distances from higher voltage lines. In the MRSP, the 88 kV power lines are usually located in the areas with high population density. Thus the observed risk could be due to other factors, such as higher exposure to benzene from heavy traffic.

An important, but unexplained, observation is a substantial risk deficit in the intermediate category in both approaches used to evaluate exposure to magnetic fields, direct measurements inside the house and distance of household to power lines. Similar dip has been observed for calculated (but not for measured fields) in previous meta-analysis [9,14].

Epidemiological studies of ELF MF and leukemia in children are difficult to be design, conduct, and interpret. There are several reasons for this – the most problematic is validity and precision in assessing exposure to ELF MF, as they vary in time and space and their assessment is difficult, especially in retrospective case–control studies. However, the rarity of childhood leukemia makes only retrospective studies feasible. The prevalence of exposure to ELF MF at levels equal to or greater than 0.3 μT in the population is very low, making it difficult to obtain reliable estimates of the potential influence of ELF MF at higher levels.

Besides the difficulty of evaluating ELF MF, many studies on the risk of childhood leukemia and ELF MF were prone to selection bias [15]. Selection bias occurs when the participation of cases and controls are different and the participation rate is correlated with exposure [16]. Depending on the type of strategy adopted for the evaluation of ELF MF, studies have reported participation rates ranging from 33% to 79%. When available the participation rate, in general, is higher in cases than controls [17]. As overall enrollment rates were low the potential for bias in our study is substantial. In addition, participating and not participating children in our study differed on number of parameters including some crude estimates of exposure, such as distance of the house to power line and ELF MF measurements in the front door.

We encountered some difficulties specifically related to studies conducted in Brazil. Due to a lack of older well organized population records, such as birth registers, we were restricted to the few years for which data was available thus leading to a small sample size. Furthermore, we were only able to include children aged eight or younger, because computerized records birth certificate records, used for control selection, were only available from 2000 forward. As a result, the cases in our study were a little younger than controls and differed from other studies, which include children 0–14 years of age.

In addition, there are several particularities that might have led to bias. It is common in Brazil for families of children with leukemia to move close to the treating hospital, and subjects who moved after diagnosis were not included as it was logistically infeasible to conduct measurements in the homes where they had lived prior to diagnosis. To address this problem, we limited some of the analysis to a stable and presumably more comparable subset. We observed higher risks when we restricted analysis to children (cases and controls) who lived in a single residence.

Finally, while adjustments for various confounders did not make a difference in most of the previous studies, the adjustment for several factors in our study had an influence on risk estimates. To the extent that evaluation of these factors is prone to bias; these adjustments are likely to be incomplete.

In conclusion, we did not observed an increased risk of ALL for children with ELF MF exposures equal or above 0.3 μT or above 0.4 μT compared to those exposed to levels lower than 0.1 μT. Increased risks were observed in some subgroup, but results were inconsistent, imprecise and included a null value. While our results are consistent with the small risks reported in other studies on ELF MF and leukemia in children, overall do not provide support for an association between magnetic fields and childhood leukemia, but small numbers and likely biases weaken the strength of this conclusion.

Conflict of interest statement

I declare to have no conflict of interest related to this paper.

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